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IPEA / AU

PCT
Demand

CHAPTER II

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
International Application No. PCT/NZ2004/000267	International Filing Date (day/month/year) 26 October 2004 (26.10.2004)
(Earliest) Priority date (day/month/year) 24 October 2003 (24.10.2003)	
Title of invention Multiple Active Agents Such As Anthelmintics Sustained Release Delivery Device	
Box No. II APPLICANT(S)	
Name and address: <u>AGRESEARCH LIMITED</u> Private Bag 5 th Floor, Tower Block, Ruakura Research Centre Centre East Street Hamilton 2020	Telephone No.: 64 7 834 6600 Facsimile No.: 64 7 834 6640 Teleprinter No.: Applicant's registration No. with the Office
State (that is, country) of nationality: New Zealand	State (that is, country) of residence: New Zealand
Name and address: <u>LEATHWICK, David Malcolm</u> 44 Williams Road RD 4 Palmerston North	
State (that is, country) of nationality: New Zealand	State (that is, country) of residence: New Zealand
Name and address: <u>MUNDAY, Rex</u> 2 McInnes Place Hamilton	
State (that is, country) of nationality: New Zealand	State (that is, country) of residence: New Zealand
<input type="checkbox"/> Further applicants are indicated on a continuation sheet	

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is agent common representative

and has been appointed earlier and represents the applicant(s) also for international preliminary examination.

is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address

WILSON, Kathryn S;

FINCH, Ian;

ROGERS, Jason P;

WELLS, Ceri P K;

MAHOOD, Tim;

SNOEP, Robert J;

MURPHY, Simon J;

KNOWLES, Andrew;

CABLE, Andrew J;

ROWELL, Simon;

ROBINSON, Carrick J;

MCMILLAN, Philip

all of Level 11, PricewaterhouseCoopers Centre, 119 Armagh Street,
P O Box 2201, Christchurch, NEW ZEALAND

Telephone No.:

64 3 379 3664

Facsimile No.:

64 9 379 8220

Teleprinter No.:

Agent's registration No. with the Office

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments: *

1. The applicant wishes the international preliminary examination to start on the basis of:

the international application as originally filed

the description as originally filed

as amended under Article 34 (pages 7-22 and 26)

the claims as originally filed

as amended under Article 19 (together with any accompanying statement)

as amended under Article 34 (pages 23-25)

the drawings as originally filed

as amended under Article 34 (Sheet 1/1)

2. The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA to postpone the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).

4. The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

which is the language in which the international application was filed.

which is the language of a translation furnished for the purposes of international search.

which is the language of publication of the international application.

which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The filing of this demand constitutes the election of all Contracting States which are designated and bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

			For International Preliminary Examining Authority use only received	not received
1. translation of international application	:	.. sheets	<input type="checkbox"/>	<input type="checkbox"/>
2. amendments under Article 34	:	21 sheets	<input type="checkbox"/>	<input type="checkbox"/>
3. copy (or, where required, translation) of amendments under Article 19	:	.. sheets	<input type="checkbox"/>	<input type="checkbox"/>
4. copy (or, where required, translation) of statement under Article 19	:	.. sheets	<input type="checkbox"/>	<input type="checkbox"/>
5. letter	:	4 sheets	<input type="checkbox"/>	<input type="checkbox"/>
6. other (specify): <i>Marked-up pages</i>	:	15 sheets	<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

1. <input checked="" type="checkbox"/> fee calculation sheet	5. <input type="checkbox"/> statement explaining lack of signature
2. <input type="checkbox"/> original separate power of attorney	6. <input type="checkbox"/> sequence listing in computer readable form
3. <input type="checkbox"/> original general power of attorney	7. <input type="checkbox"/> tables in computer readable form related to sequence listings
4. <input type="checkbox"/> copy of general power of attorney; reference number, if any:	8. <input type="checkbox"/> other (specify):

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand)

.....
SNOEP, Robert J.

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
 The applicant has been informed accordingly

4. The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5

5. Although the date of receipt of the demand is after expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82

6. The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.

7. The date of receipt of the demand is WITHIN the time limit under Rule 54bis1(a) as extended by virtue of Rule 80.5

8. Although the date of receipt of the demand is after expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82

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Demand received from IPEA on:

MARKED- UP

10/576589

1AP20 Rec'd PCT/PTO 21 APR 2006

listed components it directly references, but also other non-specified components or elements. This rationale will also be used when the term 'comprised' or 'comprising' is used in relation to one or more steps in a method or process.

5 It is an object of the present invention to address the foregoing problems or at least to provide the public with a useful choice.

Further aspects and advantages of the present invention will become apparent from the ensuing description which is given by way of example only.

DISCLOSURE OF INVENTION

10 According to one aspect of the present invention, there is provided a method of reducing parasites in animals characterised by the step of:

introducing to the animal a single delivery device containing two or more active agents selected from at least two types of anthelmintic compounds of differing chemical groups;

15 wherein the delivery device is an intra-ruminal bolus configured to release an effective amount of active agents each day for a period of between 3 and 14 days.

Preferably, the two or more anthelmintic compounds have different activities.

Preferably, the active agents are released at a substantially continuous rate.

20 According to one aspect of the present invention there is provided a method of treating animals

characterised by the step of

~~introducing to the animal a single delivery device containing two or more active agents,~~

~~wherein the delivery device is configured to release an effective amount of active agents over a defined time period of 3-14 days.~~

- 5 Preferably the treatment will be formulated to effect a reduction in the parasite burden of an animal, and for ease of reference will be referred to as such throughout the specification. However, this should not be viewed as limiting, for the treatment may alternatively involve the administration of a number of different animal remedies.
- 10 For example, it is anticipated that the present invention could be used for treating an animal with an antibiotic, antiviral or antifungal treatment, particularly when attempting to achieve increased efficacy in the treatment of bacterial and viral infectious diseases.

Such treatments may be especially useful in the treatment of animal infections
15 or animal parasites which have developed resistance standard drug treatments.

It is also anticipated that the present invention may find use in other animal treatments, such as the delivery of mineral and/or nutritional supplements, or so forth.

The term "animal" should be taken to encompass any ruminant animal in need
20 of a reduction of parasites, ~~including humans~~. The present invention is particularly suited to production animals, including but not limited to sheep, goats, cattle, deer and pigs.

For ease of reference throughout the present specification, the present

invention will be described with reference to sheep, though this should not be seen as a limitation.

~~In preferred embodiments of the present invention, the active agents will preferably be anthelmintics. For ease of reference throughout the specification,~~

- 5 ~~the active agents will be referred to as anthelmintics.~~

~~However, this should not be seen as limiting, as the active agents may include antibiotics, antiviral agents, biological agents such as living organisms, micro-organisms and/or reproductive matter thereof, therapeutic substances and/or other drug treatments.~~

- 10 The term "parasite" should be taken to include endoparasites such as helminths, nematodes, cestodes, and trematodes and combinations thereof; in addition to ectoparasites such as ticks, lice, flies, fleas and combinations thereof and so forth.

The term "anthelmintic" should be taken to mean compounds exhibiting activities selected from: nematocidal, flukicidal, trematocidal, cestocidal and/or ectoparasiticidal activities and combinations thereof, compound.

- 15
- 20 The term "effective amount" should be taken to mean the level of anthelmintics necessary to effect a reduction in the level of parasites present in an animal, including a general increase in efficacy against resistant parasites, whilst minimising the undue selection of resistance to anthelmintics and the risk of toxicity to the animal.

In preferred embodiments of the present invention the anthelmintics used may be a macrocyclic lactone such as abamectin and a benzimidazole such as albendazole.

However, once again this should not be seen as limiting and other anthelmintics could be used such as organophosphates, salicylanilide/substituted phenols, tetramisoles or pyrimidine agents. Derivatives and variations of these compounds, and their specific anti-parasitic action are well known in the art and

5 would be known to a skilled addressee.

In preferred embodiments the daily dose may be as close to the normal therapeutic (oral) dose as possible, while minimising toxicity risks. Therefore, for a given weight range of target animal, it is preferable to target the full dose to the lower end of that range.

10 Preferably, the daily dose delivered is substantially in the order of 3.0-5.0 mg/kg/day of albendazole and substantially 0.1-0.2 mg/kg/day of abamectin.

For example, for adult sheep in the range 50-80 kg it is preferable to deliver approximately 5 mg/kg of albendazole and approximately 0.2 mg/kg of abamectin to the 50 kg animal, which equates to approximately 3.125 mg/kg of

15 albendazole and approximately 0.125 mg/kg of abamectin to the 80kg animal.

It should be appreciated these dosages are given by way of example only, and should not be viewed as limiting. It is anticipated that the dose rates will vary with different anthelmintics and parasite resistance.

20 It is anticipated that daily delivery of the active agents over a period of three days will be the minimum required to cause an increase a significant increase in efficacy over standard anthelmintic compositions.

In preferred embodiments of the present invention the active agents are released each day for a defined period of time over which the anthelmintics are released is between 5 and 10 days.

The time period is also a balance between ensuring sufficient duration of exposure to ensure a significant increase in efficacy against resistant worms, whilst minimising the duration of exposure to avoid undue selection for resistance and the risks of toxicity of the anthelmintics to the animal.

- 5 It is anticipated that daily delivery of the active agents over a period of between 3 and 5 days will be the minimum required to ensure a substantial increase in efficacy over traditional anthelmintic preparations.

~~More preferably, the defined~~ Most preferably, the active agents are released each day for a period of between ~~time is 6 and 8 days.~~

- 10 Standard drenching programmes based on periods of weeks are easy to remember and calculate, making the final product user friendly. Further, such a time period allows for some variation in the delivery rates, whilst maintaining the efficacy of the treatment.

There are generally four forms of anthelmintic compositions currently available

- 15 on the market, a single dose oral liquid drench, a single dose pour-on (dermal) liquid; a single dose liquid injection and sustained controlled release devices which release a low level of anthelmintics from a solid matrix tablet encased in a plastic vehicle over an extended period of time (approximately 100 days).

Oral drenches deliver a one-off high dose of anthelmintic which kills

- 20 approximately >95% of susceptible nematodes and provides the animal with a short period of time with a low worm burden.

Pour-on and injectable formulations release the drug in response to concentration gradients. This leads to a high initial concentration of drug within the animal, which subsequently declines. Such formulations are no more

achieving extremely high efficacy against parasites, including those resistant to normal doses of single actives.

The integral in mathematics is used to "find the area enclosed by a given curve"
- in this case the area under the curve of worm exposure to anthelmintics.

- 5 To provide the maximum integral dose, the present invention may preferably utilise a controlled release device that delivers the equivalent of a high oral dose every day ~~for over~~ a period of between 3 and 14 days, long enough to provide extremely high efficacy against parasites, but not long enough to build up resistance in the worm population.
- 10 The essence of the current invention is to produce a product which delivers enhanced efficacy against most resistant worm genotypes and therefore can be used to delay the emergence of resistance to the constituent actives.

As described above, high dose levels of one or more anthelmintics have previously only been delivered to animals as a single dose, due to the practical difficulties in repetitive dosing of extensively-grazed animals. Therefore, the development of a method for delivering a maximum integral dose from a single delivery device has a number of significant advantages.

In preferred embodiments, the maximum integral dose will be delivered from a ~~short-acting (3-14 day)~~ controlled release device which releases its payload over a period of between 3 and 14 days, which is retained in the rumen of an animal by virtue of its density, and which can release multiple anthelmintic actives at a constant, high rate.

By providing a dose rate that is sufficiently high for each active to ensure increased efficacy of each against parasites resistant to that class of drug, it is

anticipated that the combination of extended duration with multiple actives will provide a very high efficacy product which will substantially delay the development of resistance.

By way of example, the inventors envisage a three active delivery device
5 containing abamectin, albendazole and tricalbendazole. The first and second actives are nematocidal, while the latter two are flukicides. Such a composition would thus provide two double combinations in a single product containing three actives.

A major impediment to others developing short-acting controlled released
10 devices has thus been the requirement for total degradation of the delivery mechanism. The delivery mechanism of the present invention may preferably be an intraruminal bolus which remains in place due to its density and which degrades completely, leaving no residue in the animal.

A number of intraruminal boluses are known in the art which could be adapted
15 for use in the present invention, such as those described in WO 95/19763 and WO 01/87273.

In some embodiments, two active agents may be incorporated into the core of an intraruminal bolus, with a third active agent in the form of a tablet added to one end of the bolus. In this manner a triple combination of active agents can
20 be delivered – the first as a result of the degradation of the tablet to give an initial dose, followed by the second and third active agents in combination released from the bolus over a period of between 3 and 14 days as described above.

Advantages of the present invention include:

single dose albendazole appears to be ineffective against immature flukes, the latter this may succumb to alter the longer-term administration of albendazole provided by the present invention.

The present invention further provides a composition, delivery means and
5 methods of manufacture thereof, for delivering an effective amount of two or
more active agents to animals over a defined period of between 3 and 14 days.

BRIEF DESCRIPTION OF DRAWINGS

Further aspects of the present invention will become apparent from the following
description which is given by way of example only and with reference to the
10 accompanying drawings in which:

Figure 1 Shows a typical dose/efficacy profile of a single dose of oral
anthelmintics;

Figure 2 Shows a typical dose/efficacy profile of a typical slow release
device, and

15 Figure 3 Shows a dose/efficacy profile of one preferred embodiment of the
present invention.

BEST MODES FOR CARRYING OUT THE INVENTION

Figure 1 shows a typical dose/efficacy profile of a single, high dose of an oral
anthelmintic. The oral dose removes greater than 95% of susceptible parasites
20 and provides the animal with a period of time with a low parasite burden.
However, this is followed by rapid re-infection.

Figure 2 shows a typical dose/efficacy profile of a current slow release device.

These devices deliver a low level of a single anthelmintic over a long period of time (100 days). It acts as a prophylactic, maintaining parasites at low levels. This limits re-infection for about 100 days. Efficacy is similar to that provided by a single oral dose as shown by Figure 1, but can require a long withholding period after use.

Figure 3 shows a dose/efficacy profile of one preferred embodiment of the present invention. Parasites are removed at a very high efficacy, with some delayed onset of re-infection and delayed resistance. The extended short duration of exposure (between 3 and 14 days) also only requires only a short withholding period after use.

Proof of concept trials

Two aspects of the present invention which increase efficacy include A) the concept of extended duration and B) the combining of multiple actives; both independently contribute to increasing efficacy.

15 **A) Extended duration.**

Proof of concept for increasing efficacy with extended duration was demonstrated in two different ways *i*) trials were conducted using repeated oral dosing to achieve extended duration thereby simulating a controlled release device and *ii*) Trials were conducted using prototype boluses releasing either 20 albendazole or abamectin, hereinafter referred to as the "Magnum" bolus. Results are given below;

i) - Trials 1 & 2 – repeated oral dosing of albendazole and abamectin in lambs to extend duration of exposure.

WHAT WE CLAIM IS:

1. A method of treating-reducing parasites in animals characterised by the step of:

introducing to the animal a single delivery device containing two or more active agents selected from at least two types of anthelmintic compounds of differing chemical groups;

wherein the delivery device is an intra-ruminal bolus configured to release an effective amount of active agents over a defined time each day for a period of between 3 and -14 days.
2. A method as claimed in claim 1 wherein the said two or more anthelmintic compounds have different activities.
3. A method as claimed in claim 1 or claim 2 wherein the active agents are released at a substantially continuous rate.
4. A method as claimed in any one of the above claims 1-3 wherein the said two or more active agents effect a reduction in the parasite burden of the animal.
5. A method as claimed in any one of the above claims 1-4 or claim 2 wherein the said two or more active agents effect a reduction in the number of resistant parasites in the animal.
6. A method as claimed in any one of claims 1 to 3 wherein the said two or more active agents are anthelmintics.
56. A method as claimed in any one of the above claims 4 wherein said anthelmintic compoundss are selected from those exhibiting activities selected from the group including: a list including-nematocidal, flukicidal,

trematocidal, cestocidal, and ectoparasiticidal activities and combinations thereof. active agents.

6. A method as claimed in claim 4 or claim 5 wherein said anthelmintics from at least two different action families.
7. A method as claimed in any one of the above claims 4 to 6 wherein said anthelmintics compounds include a macrocyclic lactone.
8. A method as claimed in claim 7 wherein the macrocyclic lactone is abamectin.
9. A method as claimed in claim 8 wherein the abamectin is delivered at a dosage of substantially 0.1 – 0.2 mg/kg/day.
10. A method as claimed in any of the above one of claims 4 to 9 wherein said anthelmintic compounds include a benzimidazole.
11. A method as claimed in claim 10 wherein the benzimidazole is albendazole.
12. A method as claimed in claim 11 wherein the albendazole is delivered at a dosage of substantially 3.0 - 5.0 mg/kg/day.
13. A method as claimed in any one of the above claims 4 to 12 wherein said anthelmintic compounds include tricalbendazole.
14. A method as claimed in any one of claims 1 to 13 wherein said two or more active agents include at least one antibiotic, antiviral or antifungal agent.
15. A method as claimed in any one of claims 1 to 14 wherein said two or

more active agents include biological agents, micro-organisms and/or reproductive matter thereof, therapeutic substances, mineral or nutritional supplements.

1614. A method as claimed in any one of the above claims 1 to 15 wherein the animal is a sheep.
1715. A method as claimed in any one of the above claims 1 to 16 wherein active agents are released each day for a the defined time period is of between 5 and- 10 days.
1816. A method as claimed in any one of the above claims 1 to 17 wherein active agents are released each day for a the defined time period of between is 6 and- 8 days.
1917. A method as claimed in any one of the above claims 1 to 18 wherein the parasite is an endoparasite selected from the group including: a-list including—helminths, nematodes, cestodes, and—trematodes, and combinations thereof.
2018. A method as claimed in any one of claims 1 to 1816 wherein the parasite is an ectoparasite selected from a-list including the group including: ticks, lice, flies, and fleas, and combinations thereof.
2119. A method as claimed in any of the above claims 1 to 20 wherein the delivery device is a controlled release device.
22. A method as claimed in claim 21 wherein the controlled release device is a ruminal bolus.
2320. A method as claimed in any one of the above claims 1 to 22 wherein the delivery device delivers a maximum integral dose.

2421. A delivery device for use in a method as claimed in any one of the above claims 1—23.

2522. The use of two or more active agents anthelmintic compounds of differing chemical groups in the manufacture of a delivery device as claimed in claim 2124.

2623. A method of treating animals substantially as described herein with reference to and as illustrated by the accompanying description and examples.

2724. A delivery device substantially as described herein with reference to and as illustrated by the accompanying description and examples.

ABSTRACT

A method of treating animals characterised by the step of introducing to the animal a single delivery device containing two or more active agents, wherein the delivery device is configured to release an effective amount of active agents each day for a over a defined time period of between 3 and-14 days.

Figure 1

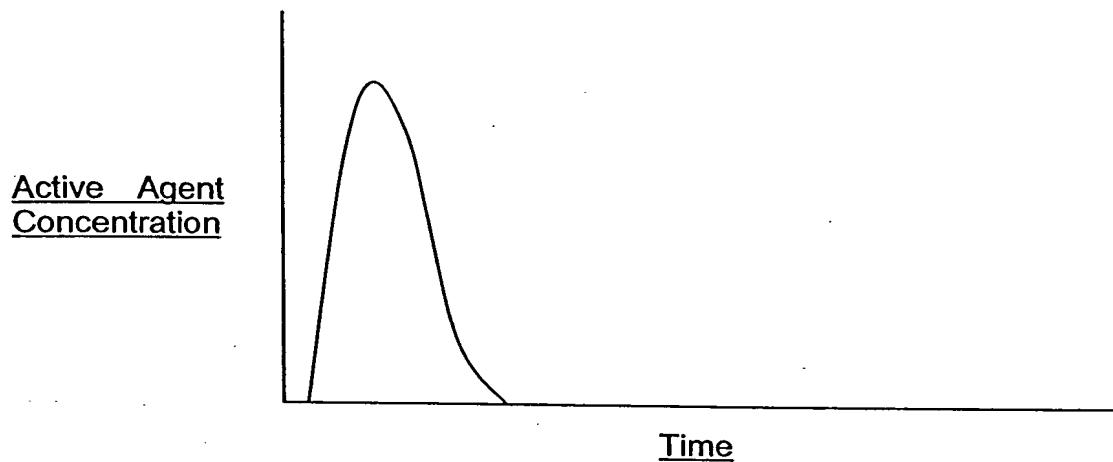


Figure 2

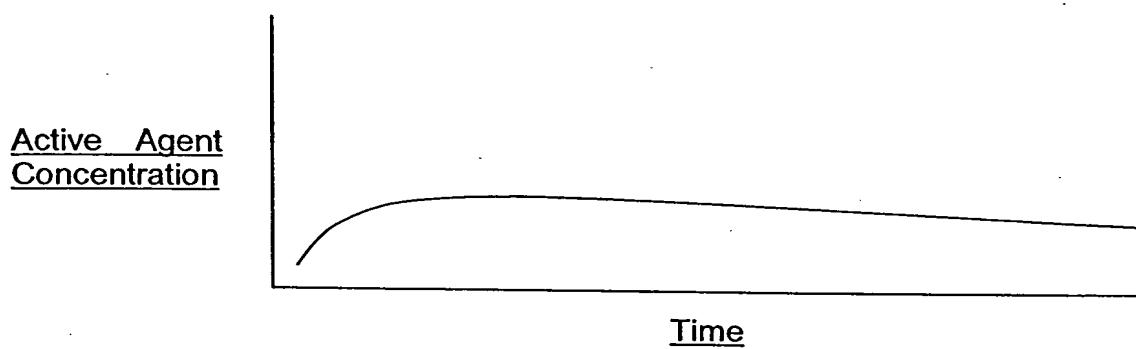
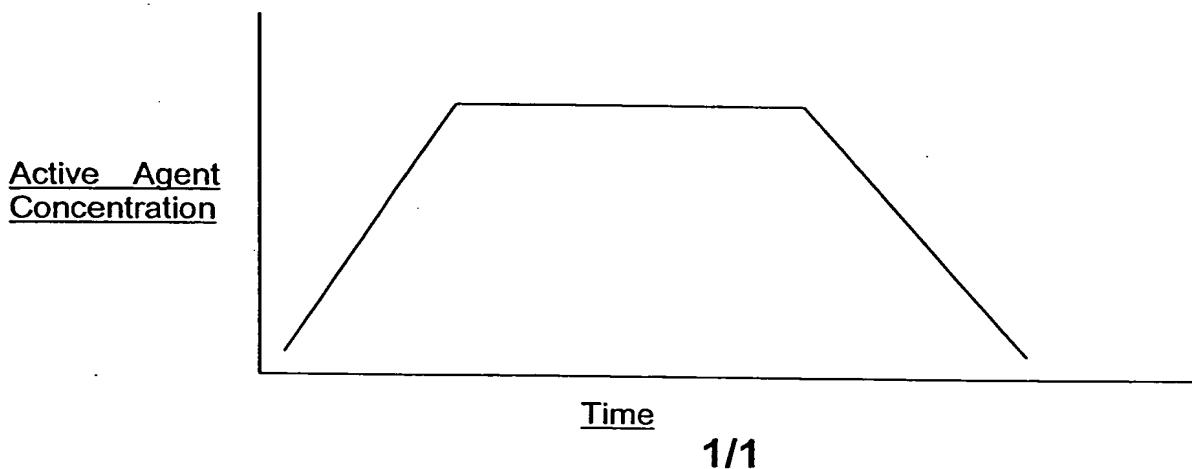


Figure 3



listed components it directly references, but also other non-specified components or elements. This rationale will also be used when the term 'comprised' or 'comprising' is used in relation to one or more steps in a method or process.

5 It is an object of the present invention to address the foregoing problems or at least to provide the public with a useful choice.

Further aspects and advantages of the present invention will become apparent from the ensuing description which is given by way of example only.

DISCLOSURE OF INVENTION

10 According to one aspect of the present invention, there is provided a method of reducing parasites in animals characterised by the step of:

introducing to the animal a single delivery device containing two or more active agents selected from at least two types of anthelmintic compounds of differing chemical groups;

15 wherein the delivery device is an intra-ruminal bolus configured to release an effective amount of active agents each day for a period of between 3 and 14 days.

Preferably, the two or more anthelmintic compounds have different activities.

Preferably, the active agents are released at a substantially continuous rate.

20 Preferably the treatment will be formulated to effect a reduction in the parasite burden of an animal, and for ease of reference will be referred to as such throughout the specification. However, this should not be viewed as limiting, for the treatment may alternatively involve the administration of a number of

different animal remedies.

For example, it is anticipated that the present invention could be used for treating an animal with an antibiotic, antiviral or antifungal treatment, particularly when attempting to achieve increased efficacy in the treatment of bacterial and
5 viral infectious diseases.

Such treatments may be especially useful in the treatment of animal infections or animal parasites which have developed resistance standard drug treatments.

It is also anticipated that the present invention may find use in other animal treatments, such as the delivery of mineral and/or nutritional supplements, or so
10 forth.

The term "animal" should be taken to encompass any ruminant animal in need of a reduction of parasites. The present invention is particularly suited to production animals, including but not limited to sheep, goats, cattle, deer and pigs.

15 For ease of reference throughout the present specification, the present invention will be described with reference to sheep, though this should not be seen as a limitation.

The term "parasite" should be taken to include endoparasites such as helminths, nematodes, cestodes, trematodes and combinations thereof; in addition to
20 ectoparasites such as ticks, lice, flies, fleas and combinations thereof.

The term "anthelmintic" should be taken to mean compounds exhibiting activities selected from: nematocidal, flukicidal, trematocidal, cestocidal and/or ectoparasiticidal activities and combinations thereof.

The term "effective amount" should be taken to mean the level of anthelmintics necessary to effect a reduction in the level of parasites present in an animal, including a general increase in efficacy against resistant parasites, whilst minimising the undue selection of resistance to anthelmintics and the risk of

5 toxicity to the animal.

In preferred embodiments of the present invention the anthelmintics used may be a macrocyclic lactone such as abamectin and a benzimidazole such as albendazole.

However, once again this should not be seen as limiting and other anthelmintics

10 could be used such as organophosphates, salicylanilide/substituted phenols, tetramisoles or pyrimidine agents. Derivatives and variations of these compounds, and their specific anti-parasitic action are well known in the art and would be known to a skilled addressee.

In preferred embodiments the daily dose may be as close to the normal

15 therapeutic (oral) dose as possible, while minimising toxicity risks. Therefore, for a given weight range of target animal, it is preferable to target the full dose to the lower end of that range.

Preferably, the daily dose delivered is substantially in the order of 3.0-5.0 mg/kg/day of albendazole and substantially 0.1-0.2 mg/kg/day of abamectin.

20 For example, for adult sheep in the range 50-80 kg it is preferable to deliver approximately 5 mg/kg of albendazole and approximately 0.2 mg/kg of abamectin to the 50 kg animal, which equates to approximately 3.125 mg/kg of albendazole and approximately 0.125 mg/kg of abamectin to the 80kg animal.

It should be appreciated these dosages are given by way of example only, and

should not be viewed as limiting. It is anticipated that the dose rates will vary with different anthelmintics and parasite resistance.

It is anticipated that daily delivery of the active agents over a period of three days will be the minimum required to cause an increase in efficacy over 5 standard anthelmintic compositions.

In preferred embodiments of the present invention the active agents are released each day for a period of between 5 and 10 days.

The time period is also a balance between ensuring sufficient duration of exposure to ensure a significant increase in efficacy against resistant worms, 10 whilst minimising the duration of exposure to avoid undue selection for resistance and the risks of toxicity of the anthelmintics to the animal.

It is anticipated that daily delivery of the active agents over a period of between 3 and 5 days will be the minimum required to ensure a substantial increase in efficacy over traditional anthelmintic preparations.

15 Most preferably, the active agents are released each day for a period of between 6 and 8 days.

Standard drenching programmes based on periods of weeks are easy to remember and calculate, making the final product user friendly. Further, such a time period allows for some variation in the delivery rates, whilst maintaining the 20 efficacy of the treatment.

There are generally four forms of anthelmintic compositions currently available on the market, a single dose oral liquid drench, a single dose pour-on (dermal) liquid; a single dose liquid injection and sustained controlled release devices

which release a low level of anthelmintics from a solid matrix tablet encased in a plastic vehicle over an extended period of time (approximately 100 days).

Oral drenches deliver a one-off high dose of anthelmintic which kills approximately >95% of susceptible nematodes and provides the animal with a

5 short period of time with a low worm burden.

Pour-on and injectable formulations release the drug in response to concentration gradients. This leads to a high initial concentration of drug within the animal, which subsequently declines. Such formulations are no more efficacious than oral formulations and have the disadvantage that the persistent

10 declining concentrations of drug favour the development of resistance (Leathwick and Sutherland 2002 *Proceedings of the 32nd Seminar, The Society of Sheep and Beef Cattle Veterinarians, N.Z. Veterinary Association*, 115-127).

Thus none of these formulations have been shown to have the potential to increase efficacy against resistant worms and/or slow the development of

15 resistance.

It has previously been shown that repeated oral dosing (daily for five days) or continuous intraruminal infusion for a period of five days can increase the efficacy of albendazole treatment.

However, repetitive dosing of extensively-grazed animals with anthelmintics is
20 not practicable. In large animals such as cattle and deer, oral drugs are also extremely difficult to administer, meaning the high majority of farmers use pour-on drenches. As the only combination products on the market are orals, there are very limited options for the use of combination products in these animals.

The available alternative to repetitive dosing is the provision of a controlled

release device. A number of studies have shown that efficacy against parasites can be increased by the provision of anthelmintics over an extended period of time, whilst requiring a lower daily level of dose than that required for a single dose.

- 5 Some controlled release devices (CRCs) are currently available that release between 1/5th and 1/10th the normal therapeutic dose (depending on animal liveweight) of either albendazole or ivermectin for 100 days. These devices act principally as prophylactics, maintaining parasites at low levels by preventing reinfection. However, such devices typically result in long withholding periods.
- 10 Recent studies also do not support the view of increased efficacy of these devices over standard oral doses. Furthermore, the prolonged delivery of small doses of anthelmintics may actually select for resistance in the worm population.

Conventional controlled release devices are made from plastic and/or metal components which remain in the animal's rumen. Obviously there is a limit to 15 the number of expired devices that can remain in an animal without consequences for the animal, and thus there is therefore a limit to how many CRCs can be given to an animal. Further, the component residues pose problems in freezing works when the offal is processed.

A second method of increasing efficacy against resistant worms is to combine 20 different action families into a single product. The principle behind this approach is that worms resistant to one active will be killed by the second active. However, until recently the only commercially available anthelmintic products which used actives in combination against the same parasite species were oral combinations of benzimidazole and levamisole. As the anthelmintic 25 classes have differing conditions of solubility and pH, it was difficult to formulate

stable compositions of other actives.

If the anthelmintic composition does not kill resistant worms the numbers of such will build up in the population. Therefore, the efficacy of any anthelmintic product against resistant worms is a key feature in delaying the development of 5 severe, production-limiting resistance.

In order to maximise the worm exposure to the anthelmintics, the applicants have developed a method of dosing animals which they have termed "maximum integral dose" and which combines high doses, extended duration and the combination of two or more anthelmintics into a single product, with the aim of 10 achieving extremely high efficacy against parasites, including those resistant to normal doses of single actives.

The integral in mathematics is used to "find the area enclosed by a given curve" - in this case the area under the curve of worm exposure to anthelmintics.

To provide the maximum integral dose, the present invention may preferably 15 utilise a controlled release device that delivers the equivalent of a high oral dose every day over a period of between 3 and 14 days, long enough to provide extremely high efficacy against parasites, but not long enough to build up resistance in the worm population.

The essence of the current invention is to produce a product which delivers 20 enhanced efficacy against most resistant worm genotypes and therefore can be used to delay the emergence of resistance to the constituent actives.

As described above, high dose levels of one or more anthelmintics have previously only been delivered to animals as a single dose, due to the practical difficulties in repetitive dosing of extensively-grazed animals. Therefore, the

development of a method for delivering a maximum integral dose from a single delivery device has a number of significant advantages.

In preferred embodiments, the maximum integral dose will be delivered from a controlled release device which releases its payload over a period of between 3
5 and 14 days, which is retained in the rumen of an animal by virtue of its density, and which can release multiple anthelmintic actives at a constant, high rate.

By providing a dose rate that is sufficiently high for each active to ensure increased efficacy of each against parasites resistant to that class of drug, it is anticipated that the combination of extended duration with multiple actives will
10 provide a very high efficacy product which will substantially delay the development of resistance.

By way of example, the inventors envisage a three active delivery device containing abamectin, albendazole and tricalbendazole. The first and second actives are nematocidal, while the latter two are flukicides. Such a composition
15 would thus provide two double combinations in a single product containing three actives.

A major impediment to others developing short-acting controlled released devices has thus been the requirement for total degradation of the delivery mechanism. The delivery mechanism of the present invention may preferably
20 be an intraruminal bolus which remains in place due to its density and which degrades completely, leaving no residue in the animal.

A number of intraruminal boluses are known in the art which could be adapted for use in the present invention, such as those described in WO 95/19763 and WO 01/87273.

In some embodiments, two active agents may be incorporated into the core of an intraruminal bolus, with a third active agent in the form of a tablet added to one end of the bolus. In this manner a triple combination of active agents can be delivered – the first as a result of the degradation of the tablet to give an 5 initial dose, followed by the second and third active agents in combination released from the bolus over a period of between 3 and 14 days as described above.

Advantages of the present invention include:

1. High efficacy even in the face of moderate levels of resistance
- 10 2. Retardation of the further development of resistance
3. Complete degradation of the device, leaving no residue in the animal
4. Combination of otherwise incompatible actives in a solid matrix
5. Although a slow release device, it will not be sufficiently long-acting to pose a serious risk to developing resistance (as with the 100 day CRCs),
15 or require a long withholding period.
6. Although a slow release device, it will deliver doses at or near the same rate as standard oral anthelmintics, significantly higher than other slow release devices, providing greater efficacy.
7. Ability to be used with large animal over 100kg, due to the ease of use
20 resulting in a viable method of delivering combination products to cattle and deer.

It is thus anticipated that the delivery method may provide increased efficacy

against parasites not normally killed effectively by a single oral dose.

Oral albendazole has a label claim for efficacy against adult liver fluke but the level of efficacy appears variable and less than desirable (Coles & Stafford 2001. *Veterinary Record* 148: 723-724.). As in the case of nematodes, 5 extended exposure of flukes to albendazole substantially increases efficacy (Kwan et al., 1988. *Journal of Controlled Release* 8: 31-38.).

Delivery of albendazole through the method of the present invention is anticipated to substantially increase efficacy against adult flukes. Further, while single dose albendazole appears to be ineffective against immature flukes, the 10 latter may succumb to the longer-term administration of albendazole provided by the present invention.

The present invention further provides a composition, delivery means and methods of manufacture thereof, for delivering an effective amount of two or more active agents to animals over a period of between 3 and 14 days.

15 **BRIEF DESCRIPTION OF DRAWINGS**

Further aspects of the present invention will become apparent from the following description which is given by way of example only and with reference to the accompanying drawings in which:

20 Figure 1 Shows a typical dose/efficacy profile of a single dose of oral anthelmintics;

Figure 2 Shows a typical dose/efficacy profile of a typical slow release device, and

Figure 3 Shows a dose/efficacy profile of one preferred embodiment of the

present invention.

BEST MODES FOR CARRYING OUT THE INVENTION

Figure 1 shows a typical dose/efficacy profile of a single, high dose of an oral anthelmintic. The oral dose removes greater than 95% of susceptible parasites
5 and provides the animal with a period of time with a low parasite burden. However, this is followed by rapid re-infection.

Figure 2 shows a typical dose/efficacy profile of a current slow release device. These devices deliver a low level of a single anthelmintic over a long period of time (100 days). It acts as a prophylactic, maintaining parasites at low levels.
10 This limits re-infection for about 100 days. Efficacy is similar to that provided by a single oral dose as shown by Figure 1, but can require a long withholding period after use.

Figure 3 shows a dose/efficacy profile of one preferred embodiment of the present invention. Parasites are removed at a very high efficacy, with some
15 delayed onset of re-infection and delayed resistance. The extended short duration of exposure (between 3 and 14 days) requires only a short withholding period after use.

Proof of concept trials

Two aspects of the present invention which increase efficacy include A) the
20 concept of extended duration and B) the combining of multiple actives; both independently contribute to increasing efficacy.

A) *Extended duration.*

Proof of concept for increasing efficacy with extended duration was

demonstrated in two different ways *i*) trials were conducted using repeated oral dosing to achieve extended duration thereby simulating a controlled release device and *ii*) Trials were conducted using prototype boluses releasing either albendazole or abamectin, hereinafter referred to as the "Magnum" bolus.

5 Results are given below;

i) - Trials 1 & 2 – repeated oral dosing of albendazole and abamectin in lambs to extend duration of exposure.

10 Table 1a & b - Percentage efficacy of albendazole against albendazole resistant parasites in lambs – efficacy based on worm count.

1a – abomasum		% reduction in worm count	
Treatment		Trichostrongylus axei	Ostertagia circumcincta
Alb - 5 mg/kg once		82.9	42.7
Alb - 5 mg/kg for 7 days		97.6	92.3
Alb - 3.75 mg/kg for 7 days		96.8	70.9
Alb - 2.5 mg/kg for 7 days		90.2	57.0
Alb - 1.75 mg/kg for 7 days		87.5	74.9

1b – small intestine		% reduction in worm count	
Treatment		Cooperia spp.	Nematodirus spp.
Alb - 5 mg/kg once		36.9	71.2
Alb - 5 mg/kg for 7 days		86.9	73.9
Alb - 3.75 mg/kg for 7 days		83.3	88.1
Alb - 2.5 mg/kg for 7 days		67.5	69.0
Alb - 1.75 mg/kg for 7 days		57.1	58.9

15 Table 2 - Percentage efficacy of abamectin against abamectin-resistant parasites in lambs – efficacy based on worm count.

Treatment	% reduction in worm count		
	Ostertagia circumcincta	Trichostrongylus colubriformis	Cooperia spp.
Aba - 0.2 mg/kg once	45.0	60.7	94.9
Aba - 0.18 mg/kg for 7 days	96.4	77.1	100.0
Aba - 0.113 mg/kg for 7 days	89.3	55.3	99.6
Aba - 0.07 mg/kg for 7 days	77.2	47.3	99.1
Moxidectin - 0.2 mg/kg once	76.3	72.5	99.1

20 These results showed that against a range of resistant parasites extending the

duration of worm exposure to drug was always as good and often far superior to administering a single oral dose. In addition the varying dose rates showed that there was often a benefit in keeping the daily dose rate as high as possible, consistent with the concept of maximum integral dose as outlined in the present specification.

ii) Trials 3 & 4 – Prototype Magnum boluses releasing albendazole in sheep and abamectin in cattle to achieve extended duration of exposure.

10 Table 3a & b - Percentage efficacy of oral albendazole and a prototype albendazole bolus against resistant parasites in adult ewes – efficacy based on worm count.

3a – abomasum	% reduction in worm count		
Treatment	Ostertagia circumcincta	Trichostrongylus axei	Haemonchus Contortus
Albendazole – 5.0 mg/kg once	59.3	91.8	91.4
Albendazole bolus	86.9	92.5	98.7

3b – small intestine	% reduction in worm count
Treatment	Cooperia spp.
Albendazole – 5.0 mg/kg once	59.3
Albendazole bolus	86.9

15 Table 4 – Percentage efficacy of pour-on abamectin, pour-on eprinomectin and a prototype Magnum bolus releasing abamectin against resistant Cooperia oncophora in cattle

	% reduction in worm count
Treatment	Cooperia oncophora.
Abamectin pour-on	81.0
Eprinomectin pour-on	83.6
Abamectin bolus	97.4

20

B) Combining actives.

Efficacy data for combining Benzimidazole and Levamisole actives against resistant parasites is reasonably common. Further, there is considerable evidence that these actives work independently and so it can be expected their 5 combined efficacies will work in an additive manner (Anderson et al. 1991. *Australian Veterinary Journal* 68, 133-136.). Hence the expected efficacy of combining two or more actives can be calculated and compared with the measured value.

e.g. Farm 4 from Anderson et al, 1991

10	Efficacy of Levamisole	88%
	Efficacy of albendazole	73%
	Efficacy of Levamisole + albendazole	95%
	Efficacy expected based on additive effects	97%

15 Data on combining the benzimidazole and macrocyclic lactone classes of actives (as is proposed in this specification) is harder to find, but some does exist for goats:

e.g. Data from Pomroy et al, 1992 (*New Zealand Veterinary Journal* 40, 76-78.)

20	Efficacy of ivermectin	27%
	Efficacy of oxfendazole	82%
	Efficacy of ivermectin + oxfendazole	97%
	Efficacy expected based on additive effects	87%

This concept has again been tested for the present invention by constructing and testing for efficacy a Magnum bolus releasing 2 actives simultaneously. A prototype sheep bolus designed to release 5 mg/kg of albendazole and 0.18

mg/kg abamectin in a 50 kg sheep was tested against two species of multiple drench resistant parasites. Trial lambs ranged in weight from 48 – 55.5 kg.

5 Table 5: Efficacy based on worm counts of a Magnum combination bolus (albendazole + abamectin), single standard oral doses of both albendazole and abamectin and moxidectin oral against multiple drug resistant *Ostertagia* and *Trichostrongylus* in sheep.

Treatment group	<i>Ostertagia circumcincta</i>	<i>Trichostrongylus colubriformis</i>
Magnum combination bolus	99.1	100
Albendazole oral + abamectin oral	38.9	94.0
Moxidectin-oral	59.9	90.6

Conclusion:

10 The results show a substantial increase in efficacy of the Magnum bolus over a combination of the same actives administered as two single oral doses. This supports the anticipated synergy which is the foundation of the present invention, i.e. extended delivery of each active gives increased efficacy, but by combining multiple actives an even greater step up in efficacy is achieved
15 against resistant worms. This can also been seen in the comparison with moxidectin which although only a single active is recognised as the most potent single active product on the market.

C) Efficacy against flukes (*Fasciola hepatica*).

20 To test the efficacy of prolonged exposure to albendazole against liver fluke a trial was conducted using an albendazole only bolus in sheep. Sheep from a commercial farm with a previous history of fluke infections were screened by faecal egg count to identify animals carrying fluke infections.

These animals were then randomly allocated to one of two treatment groups on

the basis of these egg counts and one group was administered a magnum bolus releasing 5 mg/kg in a 50 kg animal. Twenty days after treatment all animals were slaughtered and livers recovered for fluke counts. Mean numbers of flukes recovered were 12.8 and 2.0 from the control and treated groups 5 respectively, equating to an 84% reduction as a result of treatment.

Thus treatment with the Magnum bolus containing albendazole has resulted in a measureable efficacy against liver flukes.

Aspects of the present invention have been described by way of example only and it should be appreciated that modifications and additions may be made 10 thereto without departing from the scope thereof as defined in the appended claims.

WHAT WE CLAIM IS:

1. A method of reducing parasites in animals characterised by the step of:
introducing to the animal a single delivery device containing two or more active agents selected from at least two types of anthelmintic compounds of differing chemical groups;
wherein the delivery device is an intra-ruminal bolus configured to release an effective amount of active agents each day for a period of between 3 and 14 days.
2. A method as claimed in claim 1 wherein the said two or more anthelmintic compounds have different activities.
3. A method as claimed in claim 1 or claim 2 wherein the active agents are released at a substantially continuous rate.
4. A method as claimed in any one of the above claims wherein the said two or more active agents effect a reduction in the parasite burden of the animal.
5. A method as claimed in any one of the above claims wherein the said two or more active agents effect a reduction in the number of resistant parasites in the animal.
6. A method as claimed in any one of the above claims wherein said anthelmintic compounds are selected from those exhibiting activities selected from the group including: nematocidal, flukicidal, trematocidal, cestocidal, ectoparasiticidal activities and combinations thereof.

7. A method as claimed in any one of the above claims wherein said anthelmintic compounds include a macrocyclic lactone.
8. A method as claimed in claim 7 wherein the macrocyclic lactone is abamectin.
9. A method as claimed in claim 8 wherein the abamectin is delivered at a dosage of substantially 0.1 – 0.2 mg/kg/day.
10. A method as claimed in any of the above claims wherein said anthelmintic compounds include a benzimidazole.
11. A method as claimed in claim 10 wherein the benzimidazole is albendazole.
12. A method as claimed in claim 11 wherein the albendazole is delivered at a dosage of substantially 3.0 - 5.0 mg/kg/day.
13. A method as claimed in any one of the above claims wherein said anthelmintic compounds include tricalbendazole.
14. A method as claimed in any one of the above claims wherein the animal is a sheep.
15. A method as claimed in any one of the above claims wherein active agents are released each day for a period of between 5 and 10 days.
16. A method as claimed in any one of the above claims wherein active agents are released each day for a period of between 6 and 8 days.

17. A method as claimed in any one of the above claims wherein the parasite is an endoparasite selected from the group including: helminths, nematodes, cestodes, trematodes, and combinations thereof.
18. A method as claimed in any one of claims 1 to 16 wherein the parasite is an ectoparasite selected from the group including: ticks, lice, flies, fleas, and combinations thereof.
19. A method as claimed in any of the above claims wherein the delivery device is a controlled release device.
20. A method as claimed in any one of the above claims wherein the delivery device delivers a maximum integral dose.
21. A delivery device for use in a method as claimed in any one of the above claims.
22. The use of two or more anthelmintic compounds of differing chemical groups in the manufacture of a delivery device as claimed in claim 21.
23. A method of treating animals substantially as described herein with reference to and as illustrated by the accompanying description and examples.
24. A delivery device substantially as described herein with reference to and as illustrated by the accompanying description and examples.

ABSTRACT

A method of treating animals characterised by the step of introducing to the animal a single delivery device containing two or more active agents, wherein the delivery device is configured to release an effective amount of active agents each day for a time period of between 3 and 14 days.

Figure 1

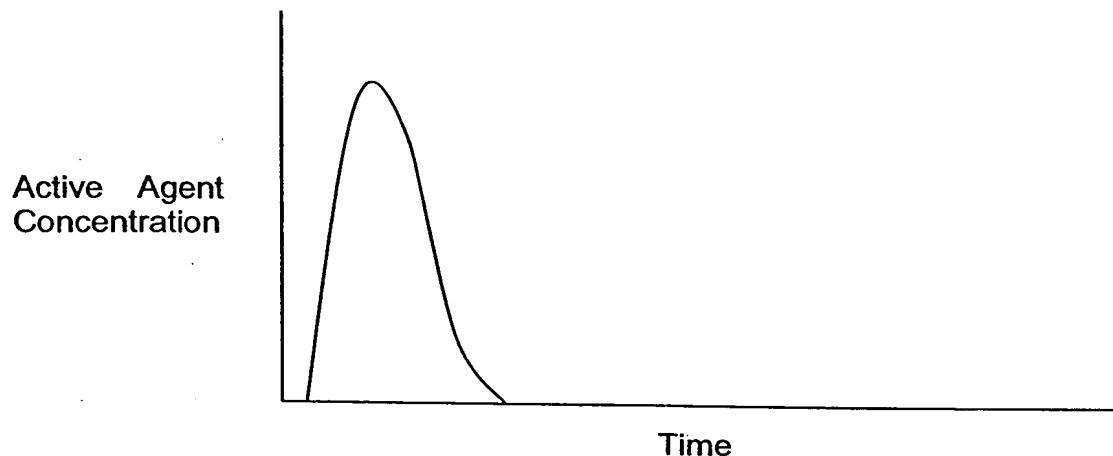


Figure 2

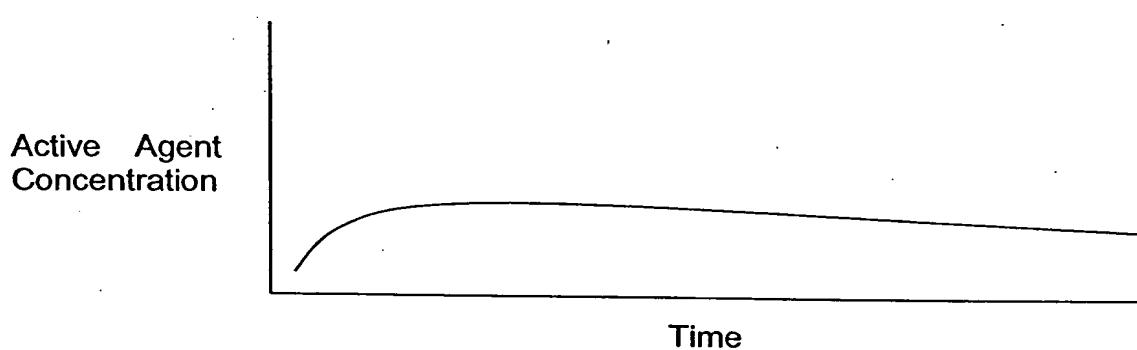
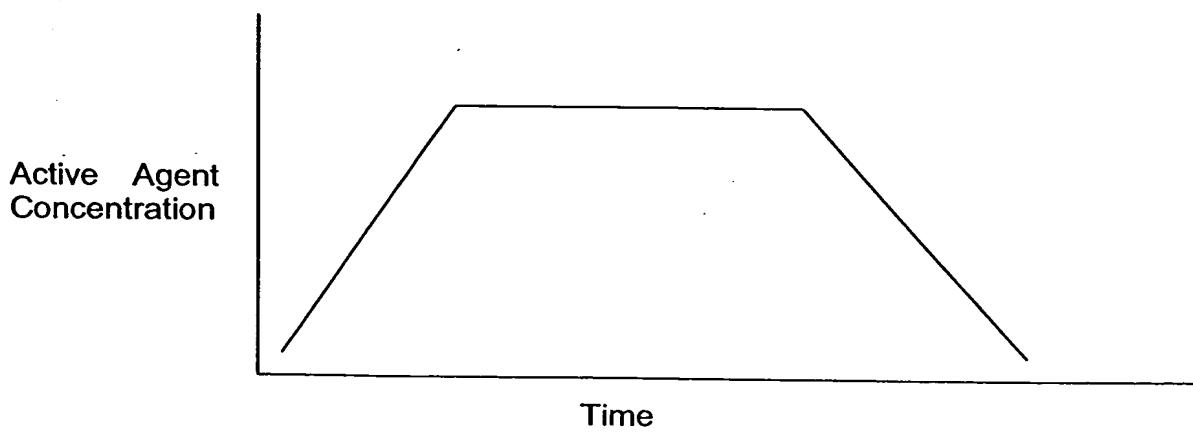


Figure 3



1/1